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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/536,560	12/20/2005	Itzhak Bentwich	050992.0300.13USPC	9481

37808 7590 01/06/2010

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ART UNIT	**PAPER NUMBER**
1635	

MAIL DATE	DELIVERY MODE
01/06/2010	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/536,560	BENTWICH, ITZHAK	
	Examiner	Art Unit	
	DANA SHIN	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06 November 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *21-48 and 50-55* is/are pending in the application.

4a) Of the above claim(s) *35-48,51,54 and 55* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *21-34,50,52 and 53* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on November 6, 2009 has been entered.

Status of Claims

Claims 21-48 and 50-55 are currently pending in the instant application. Claims 35-48, 51, 54-55, and SEQ ID NOs:1-2078, 2080-3353 have previously been withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to nonelected inventions, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on August 18, 2008. Accordingly, claims 21-34, 50, and 52-53 are under examination on the merits in the instant case.

Response to Arguments and Amendments

Any rejections not repeated in this Office action are hereby withdrawn in view of the arguments/amendment filed on November 6, 2009.

Priority

Applicant's claim for the benefit of a prior-filed application under 35 U.S.C. 119(e) or under 35 U.S.C. 120, 121, or 365(c) is acknowledged. Applicant has not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. 119(e) or 121 as follows:

The later-filed application must be an application for a patent for an invention which is also disclosed in the prior application (the parent or original nonprovisional application or provisional application). The disclosure of the invention in the parent application and in the later-filed application must be sufficient to comply with the requirements of the first paragraph of 35 U.S.C. 112. See *Transco Products, Inc. v. Performance Contracting, Inc.*, 38 F.3d 551, 32 USPQ2d 1077 (Fed. Cir. 1994).

None of the disclosure of the prior-filed applications provides adequate support or enablement in the manner provided by the first paragraph of 35 U.S.C. 112 for one or more claims of this application, because none discloses the claimed molecule structure, let alone SEQ ID NO:2079. Hence, the earliest effective filing date for claims 21-34, 50, and 52-53 will be the filing date of PCT/IL03/00998, filed on November 26, 2003. If applicant believes that any of the prior-filed applications provide adequate support for claims 21-34, 50, and 52-53, applicant is advised to provide the particulars in response to this Office action.

Claim Objections

Claim 21 is objected to because of the following informalities:

Claim 21, line 8 recites "the two stem segments each consist of 14-71 nucleotides". It appears that the word "consist" should be "consists" for grammatical correction. Appropriate correction is required.

Claim 21, line 10 recites "the first and second stem segment are". It appears that the word "segment" should be "segments" for grammatical correction. Appropriate correction is required.

Claim 21, line 18 recites "the first and second viral nucleic acid are". It appears that the word "acid" should be "acids" for grammatical correction. Appropriate correction is required.

Claim 50 is objected to for containing non-elected subject matter.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 21-34, 50, and 52-53 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The claims are directed to "An isolated first viral nucleic acid or complement thereof". As such, the claims are directed to a single, only one nucleic acid. However, the claims recite two different nucleic acids: a first nucleic acid and a second nucleic acid. As currently written and claimed, the claims do not particularly point out why the second nucleic acid is recited in the claims that are only directed to the first nucleic acid. Hence, one of ordinary skill in the art cannot determine the structural/functional relationship between the first nucleic acid and the

second nucleic acid because the claimed subject matter relates to only the first nucleic acid, not the second nucleic acid. As such, the claim language as currently presented imparts ambiguity, thereby rendering the nature of the claimed subject matter indefinite.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 21-22, 25, and 33-34 are rejected under 35 U.S.C. 102(e) as being anticipated by Zamore et al. (US 2006/0009402 A1, citation of record).

The instant claims are written as product-by-process claims. Applicant's attention is directed to MPEP 2113 that teaches the following: "Even though the product-by-process claims are limited by and defined by the process, determination of patentability is based on the product itself. The patentability is based on the product itself. The patentability of a product does not depend on its method of production."

Zamore et al. teach isolated miRNA precursors (about 100 nucleotides or longer in length, for example 72 nucleotides (see SEQ ID NO:1)), which comprise two stem portions (about 18-19 or 22 or 25 nucleotides in length) that are partially complementary and are

connected by a hairpin loop portion (about 3 or 15 or 20 nucleotides in length). They teach that the stem portions comprise a mature miRNA, which binds and targets a portion of the mRNA of a target gene and inhibits translation of the mRNA, thereby inhibiting the expression of the mRNA. They teach that the target gene of the miRNA is a viral gene or viral genes. They teach that one can express miRNA precursors or miRNAs by incorporating them into an vector. See paragraphs 0006-0009, 0041-0043; claims 1-41, 55-56. Since mature miRNA (the first nucleic acid) of Zamore et al. meets the structural limitations set forth in the claims, the claims are anticipated by Zamore et al.

Claims 21-22, 25, and 33-34 are rejected under 35 U.S.C. 102(e) as being anticipated by Cullen et al. (US 2004/0053411 A1, citation of record).

Cullen et al. teach isolated nucleic acids that encode miRNA precursors that comprise mature miRNAs, which induce degradation of the mRNA transcript of a target gene sequence or inhibit the translation of the mRNA, wherein the target gene includes viral RNA. They teach that mature miRNAs are about 19-24 nucleotides in length and complementary to the target sequence within the mRNA. They teach that isolated miRNAs can be designed to target the 3'-UTR or the 5'-UTR of the mRNA. They teach that miRNA precursors are 40-100 nucleotides or preferably 50-75 nucleotides in length, which includes a loop sequence of 6-15 nucleotides in length. They teach vectors comprising miRNA precursors. See paragraphs 0019-0025, 0029; claim 27. Since the mature miRNAs of Cullen et al. meet the structural limitations set forth in the claims, the claims are anticipated by Cullen et al.

Claims 21-22, 33-34, 50, 52 are rejected under 35 U.S.C. 102(e) as being anticipated by Lin et al. (US 2004/0253604 A1).

Lin et al. teach that an stRNA or miRNA located in the intronic, non-coding region of a chemokine inhibits an HIV-1 genomic sequence and reduces HIV-1 subtype B gene activity. See paragraph 0039. Accordingly, all structural and functional requirements set forth in the claims are met by the teachings of Lin et al. and thus the stRNA or miRNA of Lin et al. is a "first viral nucleic acid" claimed in the instant case, absent evidence to the contrary. That is, the mere naming of the claimed first nucleic acid "viral" or the recitation that the first nucleic acid is isolated from the genome of a virus does not patentably distinguish the stRNA or miRNA that inhibits HIV-1 of Lin et al. from the claimed "viral" nucleic acid because the determination of patentability for product claims is based on the product itself and because the word "viral" can be broadly and reasonably interpreted to define the function of the first nucleic acid such that the nucleic acid inhibits viral expression.

Claims 21-22, 33-34, 50, and 52 are rejected under 35 U.S.C. 102(e) as being anticipated by Khvorova et al. (US 2007/0031844 A1, citation of record).

It is noted that the claims are in no way limited to a miRNA, let alone a miRNA comprising a nucleotide sequence that is isolated from a viral genomic sequence. That is, the claims as currently written embrace any nucleic acid as long as it consists of 15-24 nucleotides and is at least 40.9% complementary to target mRNA (structural limitations) and is capable of binding and inhibiting target mRNA (functional limitations).

Note that the recitations of "viral nucleic acid" and "isolated from the genome of virus" do not limit the nucleic acids claimed in claims 21-22, 33-34 and 50 to a nucleic acid isolated from a viral sequence because one cannot know whether a given nucleic acid is isolated from virus thus being "viral" when merely looking at the synthetic, isolated product of a nucleotide sequence of the given nucleic acid, and therefore the word "viral" cannot define the actual structure of the nucleic acid claimed in the instant case (for example, one cannot know whether a nucleic acid sequence of GGAAGGACGGGAAGUGGAA is isolated from a virus or functionally viral by looking at the nucleic acid sequence), and because the procedural phrase "isolated from the genome of virus" does not define the product claimed in the instant case.

Khvorova et al. teach a nucleic acid that is 19 nucleotides in length and at least 72.7% identical to the nucleotide sequence of SEQ ID NO:2079. See SEQ ID NO:1360090 and below for sequence alignment. They also teach that the nucleic acid can be inserted into a vector. They teach that one can use SEQ ID NO:1360090 to inhibit target mRNA. See paragraph 0266.

```
Qy          2 GGAAGGACGGGAAGUGGAA 20
              | ||||| ||||||||||||
Db          1 GCAAGGAAGGGAAGUGGAA 19
```

Since the nucleic acid of Khvorova et al. meets the structural and functional requirements set forth in the claims, the nucleic acid of SEQ ID NO:1360090 of Khvorova et al. is a "first viral nucleic acid", absent evidence to the contrary.

Claims 21-22, 33-34, 50, and 52 are rejected under 35 U.S.C. 102(e) as being anticipated by Usman et al. (US 2005/0124568 A1).

Usman et al. disclose a 19-mer antisense nucleic acid of SEQ ID NO:716, which is a "complement" of SEQ ID NO:2079 with a high sequence homology as shown below:

```
Qy          2 GGAAGGACGGGAAGUG 17
              ||||||||||||  |:|
Db         16 GGAAGGACGGGATGTG 1
```

They teach that the antisense nucleic acid is capable of binding and inhibiting target mRNA of acetyl-CoA-Carboxylase. They teach that SEQ ID NO:716 can be expressed from an expression vector or can be used as a probe. See paragraphs 0068, 0233, 0414-0415; Table II on page 62. Since the structural and functional limitations of SEQ ID NO:716 correspond to those set forth in the instant claims, the nucleic acid of SEQ ID NO:716 of Usman et al. is a " first viral nucleic acid", absent evidence to the contrary.

Claims 21-22, 33, 50, and 52 are rejected under 35 U.S.C. 102(b) as being anticipated by Stacey et al. (WO 00/31540 A1, citation of record).

Stacey et al. disclose a 20-mer nucleic acid of SEQ ID NO:10, which is at least 40.9% complementary to the mRNA encoding PU-1 and is significantly homologous to the nucleotide sequence of SEQ ID NO:2079 as shown below. They teach that SEQ ID NO:10 can be used as a probe.

```
Qy          3 GAAGGACGGGAAGUGGAAGU 22
              | ||||| ||||||:|| ||:
Db          1 GTAGGACCGGAAGTGGGAGT 20
```

Note that the claimed first viral nucleic acid is a bioinformatically identified nucleotide sequence and that the functional limitation of "capable of inhibiting expression of a protein encoded by a mRNA" recited in the claims is not actually demonstrated by the instant

specification. Thus, the function of the nucleic acid of Stacey et al. is as enabling as that of the nucleic acid claimed in the instant application such that the nucleic acid of SEQ ID NO:10 of Stacey et al. would, necessarily and inherently, be as capable as the nucleic acid of the instant application of inhibiting target expression because the nucleic acid of Stacey et al. meets the structural limitations of the "first" nucleic acid claimed in the instant case, absent evidence to the contrary. Also note that when a rejection is based on a reference teaching a product appearing to be substantially identical to the claimed product, and when the examiner presents reasoning tending to show inherency, the burden shift to the applicant to show an unobvious difference. See MPEP 2112: "[T]he PTO can require an applicant to prove that the prior art products do not necessarily or inherently possess the characteristics of his [or her] claimed product. Whether the rejection is based on inherency' under 35 U.S.C. 102, on prima facie obviousness' under 35 U.S.C. 103, jointly or alternatively, the burden of proof is the same...[footnote omitted]."

Accordingly, the instantly claimed nucleic acid is anticipated by the nucleic acid of SEQ ID NO:10 of Stacey et al.

Claims 21-22, 33, 50, and 52 are rejected under 35 U.S.C. 102(b) as being anticipated by Berlin et al. (WO 02/077272 A2).

Note that the claims read on both the first nucleic acid and a "complement" of the first nucleic acid.

Berlin et al. disclose a 18-mer nucleic acid of SEQ ID NO:1247 that is highly homologous to SEQ ID NO:2079 claimed in the instant case. See below for the sequence alignment.

```
Qy          4 AAGGACGGGAAGUGG 18
              |||| ||||||| :||
Db          4 AAGGGCGGGAAGTGG 18
```

They also disclose a 18-mer nucleic acid of SEQ ID NO:1249, which is highly complementary to SEQ ID NO:2079 as shown in the sequence alignment below:

```
Qy          4 AAGGACGGGAAGUGG 18
              |||| ||||||| :||
Db         15 AAGGGCGGGAAGTGG 1
```

The nucleic acid of SEQ ID NO:1249 is also complementary to a target mRNA encoding nuclear prelamin A recognition factor-like (NARFL) and thus is capable of inhibiting NARFL expression. See the sequence alignment between SEQ ID NO:1249 of Berlin et al. and nucleotides 108-122 of NARFL (NM_022493).

```
Query  1    CCACTTCCCGCCCTT  15
            ||||||||||||||||
Sbjct  122  CCACTTCCCGCCCTT  108
```

They teach that SEQ ID NO:1247 or SEQ ID NO:1249 can also be used as a diagnostic probe. See pages 12-13, 75, 79-80; claims 34, 39, 52. Since all structural requirements for the first nucleic acid and the complement of the first nucleic acid are met by SEQ ID NO:1247 and SEQ ID NO:1249 of Berlin et al., the claims are anticipated by Berlin et al.

Claims 21-22, 33, 50, and 52 are rejected under 35 U.S.C. 102(b) as being anticipated by Baker et al. (US 6,399,297 B1).

Baker et al. disclose an 18-mer nucleic acid of SEQ ID NO:101 (ISIS-26808), which is significantly homologous to the "complement" of SEQ ID NO:2079 of the instant application. See the sequence alignment below:

```
Qy           6 GGACGGGAAGUGGAAG 21
               |||||||| | |||||
Db          18 GGACGGGATGGGGAAG 3
```

Baker et al. teach that ISIS-26808 is completely complementary to TRAF-3 mRNA and inhibits TRAF-3 expression. They teach that ISIS-26808 can also be used as a diagnostic probe for studying gene function. See columns 2, 5-6, 10, 29. Since the ISIS-26808 nucleic acid compound meets the structural as well as functional requirements set forth for the first nucleic acid, the claims are anticipated by Baker et al.

Claims 21-22, 33, 50, and 52 are rejected under 35 U.S.C. 102(b) as being anticipated by Lieven et al. (US 6,087,093).

Lieven et al. disclose a 15-mer nucleic acid of SEQ ID NO:28 that is complementary to a HIV reverse transcriptase gene fragment, which can be used as a probe (see Table 3), wherein the 15-mer nucleic acid is highly homologous to SEQ ID NO:2079 as shown below:

```
Qy           5 AGGACGGGAAGUGGA 19
               || || ||||| |||
Db           1 AGAACTGGAAGAGGA 15
```

Since all structural limitations of the claimed first nucleic acid are met by SEQ ID NO:28 of Lieven et al., the 15-mer nucleic acid would necessarily and inherently have the capability of inhibiting target expression, absent evidence to the contrary.

Claim 21 and 52 are rejected under 35 U.S.C. 102(b) as being anticipated by Zhu et al. (*Journal of General Virology,* 1992, 73:1309-1312).

Zhu et al. disclose a nucleic acid isolated from nucleotides 1010-1055 of the intergenic, non-coding region of a rice stripe virus isolate T RNA 4 (RSV-T RNA 4), wherein the nucleic acids contains a "first viral nucleic acid" of 18-24 nucleotides. Since the structural requirements for the claimed first viral nucleic acid are met by the two nucleic acids of Zhu et al. depicted in Figure 2, they would necessarily and inherently be capable of binding to and inhibiting target mRNA, absent evidence to the contrary.

Claim 21 and 52 are rejected under 35 U.S.C. 102(b) as being anticipated by Ghiringhelli et al. (*Journal of General Virology,* 1991, 72:2129-2141).

Ghiringhelli et al. disclose two nucleic acids isolated from the intergenic, non-coding region of a Junin virus S RNA, wherein the two nucleic acids each contains a "first viral nucleic acid" of 15-24 nucleotides or 18-24 nucleotides. Since the structural requirements for the claimed first viral nucleic acid are met by the two nucleic acids of Ghiringhelli et al. depicted in Figure 6, they would necessarily and inherently be capable of binding to and inhibiting target mRNA, absent evidence to the contrary.

Claim 21 and 52 are rejected under 35 U.S.C. 102(b) as being anticipated by Baumstark et al. (*RNA,* 2001, 7:1652-1670).

Baumstark et al. discloses nucleic acids isolated from the intergenic regions of bromovirus (BMV) RNA3, CMV subgroups I and II, and TAV, wherein each of the nucleic acids has a hairpin structure and comprises a "first viral nucleic acid" of 15-24 nucleotides or 18-24 nucleotides. Since the structural requirements for the claimed first viral nucleic acid are met

by the nucleic acids disclosed by Baumstark et al. depicted in Figure 7, they would necessarily and inherently be capable of binding to and inhibiting target mRNA, absent evidence to the contrary.

Claim 21 and 52-53 are rejected under 35 U.S.C. 102(b) as being anticipated by Ozdarendeli et al. (*Journal of General Virology,* 2001, 75:7362-7374).

Ozdarendeli et al. discloses nucleic acids isolated from the intergenic region of bovine coronavirus, wherein the nucleic acids have a stable stem-loop hairpin secondary structure and comprise a "first viral nucleic acid" of 18-24 nucleotides. Since the structural requirements for the claimed first viral nucleic acid are met by the nucleic acids disclosed by Ozdarendeli et al. depicted in Figure 2A, they would necessarily and inherently be capable of binding to and inhibiting target mRNA, absent evidence to the contrary.

Claim 21 and 52-53 are rejected under 35 U.S.C. 102(b) as being anticipated by Davison et al. (*Journal of General Virology,* 1985, 66:207-220).

Davison et al. disclose a hairpin nucleic acid isolated from the non-coding intergenic region of HSV-1 and a hairpin nucleic acid isolated from the non-coding intergenic region of VZV, wherein each of the two hairpin nucleic acids contains a "first viral nucleic acid" of 18-24 nucleotides. Since the structural requirements for the claimed first viral nucleic acid are met by the two nucleic acids of Davison et al. depicted in Figure 6, they would necessarily and inherently be capable of binding to and inhibiting target mRNA, absent evidence to the contrary.

Response to Arguments

Applicant's arguments with regard to the rejections based on Zamore et al. (US 2006/0009402 A1), Cullen et al. (US 2004/0053411 A1), and Khvorova et al. (US 2007/0031844 A1) filed on November 6, 2009 have been fully considered but they are not persuasive. Applicant argues that the recitation of the newly added limitation "wherein the first and second viral nucleic acids are isolated from the genome of a virus." is sufficient to overcome the 102(e) rejections of record because the nucleic acids of Zamore et al., Cullen et la., or Khvorva et al. are not isolated from viral genomes. Contrary to applicant's argument, the newly added "process" step does not patentably distinguish the nucleic acids of Zamore et al., Cullen et la., or Khvorva et al. from the claimed first nucleic acid because patentability determination for product-by-process claims is based on the product itself. See MPEP 2113 that teaches the following: "Even though the product-by-process claims are limited by and defined by the process, determination of patentability is based on the product itself. The patentability is based on the product itself. The patentability of a product does not depend on its method of production." Accordingly, the 102(e) rejections previously applied in the last Office action are hereby reapplied herein.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 21-34, 50, and 52-53 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lai et al. (*Genome Biology,* 2003, 4:1-20, citation of record) in view of Zhu et al. (*Journal of General Virology,* 1992, 73:1309-1312), Ghiringhelli et al. (*Journal of General Virology,* 1991, 72:2129-2141), Baumstark et al. (*RNA,* 2001, 7:1652-1670), Ozdarendeli et al. (*Journal of General Virology,* 2001, 75:7362-7374), Davison et al. (*Journal of General Virology,* 1985, 66:207-220), and Perry et al. (*Journal of General Virology,* 1988, 69:2831-2846).

Lai et al. characterize the year of 2003 is "heady times of miRNA gene discovery" (see page 16) and teach a computational, bioinformatics-based strategy of identifying miRNAs (small non-coding RNAs or about 21-22 nucleotides) and miRNA precursor sequences, which is named "miRseeker" that incorporates an RNA folding algorithm, wherein miRNAs have been previously known to constitute about 1% of protein-coding sequences of vertebrates and are found to constitute about 1% of "predicted protein-coding genes in *Drosophila*." as concluded by Lai et al. See the abstract. That is, they teach that a computational, bioinformatics-based approach based the structural features of known miRNAs combined with comparative genomics allows one to discover unknown miRNAs "in a given sequenced genome". See page 16. They

teach that they identified 48 novel miRNA candidates by using their computational "miRseeker" method, wherein 32 are newly verified. They teach that one can experimentally verify the computationally identified miRNAs by performing expression profile assays. They also teach that miRNAs can be identified by "direct cloning of mature 21-22 nucleotide RNAs, either from size-elected total RNA or from purified miRNP complexes." See page 15. They teach that miRNAs repress target mRNA translation by binding to the partially complementary nucleotide sequence located within the 3' UTR or the target mRNA. See the entire reference including Figures 2-4 and Table 1. Lai et al. do not teach miRNAs identified in a viral genome using their bioinformatics-based "miRseeker" program.

Zhu et al. teach that the non-coding intergenic region (nucleotides 591-1245) of a rice stripe virus isolate T RNA 4 (RSV-T RNA 4) contains small hairpin structures. See the entire reference including Figure 2.

Ghiringhelli et al. teach that the non-coding intergenic region of a Junin virus S RNA contain small hairpin structures. See the entire reference including Figure 6.

Baumstark et al. teach that intergenic regions of bromovirus (BMV) RNA3, CMV subgroups I and II, TAV, and PSV contain small hairpin structures. See the entire reference including Figure 7.

Ozdarendeli et al. teach that the intergenic region of 199-nucleotides in length of bovine coronavirus contains two nucleic acids forming a stable stem-loop hairpin secondary structure that is predicted by the Zucker algorithm. See the entire reference including Figure 2A.

Davison et al. teach that the intergenic region of the genomes of varicella-zoster virus (VZV) and herpes simplex virus type 1 (HSV-1) contains stable hairpin structures wherein the

two stem regions are partially complementary and comprise about 22-24 nucleotides. See the entire reference including Figure 6.

Perry et al. teach that the complete genomic sequence of the human herpes virus type 1 (HHV-1), also known as human simplex virus 1 (HSV-1), has been sequenced. They disclose the genomic sequence of the HSV-1 which comprises both protein coding and non-coding sequences of U_L and IR_L (UL54, UL55, UL56, LAT, IE110), wherein the DNA sequence of nucleotides 118330-118351 (see Figure 2 on page 2834) within one of the non-coding intergenic regions is found to correspond to the RNA sequence of SEQ ID NO:2079 claimed in the instant case.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to utilize a computational algorithm-based bioinformatics methodology to identify potential miRNAs located within the non-coding regions of viral genomes such as the non-coding regions of the HSV-1 of Perry et al. and isolate miRNAs from the HSV-1 genome.

One of ordinary skill in the art would have been motivated to do so with a reasonable expectation of success so as to use the isolated miRNAs as a repressor of target mRNA translation, which is useful to study the functions of the target mRNA/protein, because it was known in the art that miRNAs generally function to repress target translation by binding to the 3' UTR of the target mRNA, and because computational algorithm-based bioinformatics approaches to identify new miRNAs in a given genomic sequence that is available in the art were known to be effective, and because miRNAs were known to be located within the non-coding regions of a genomic sequence, and because the entire genomic sequence including coding and non-coding regions of the HSV-1 was available in the art at the time the invention was made. Since small non-coding RNAs located within the non-coding intergenic regions of a number of

various viral genomic sequences (e.g., RSV-T RNA 4, Junin virus S RNA, BMV RNA3, CMV subgroups I and II, TAV, bovine coronavirus, VZV, and HSV-1) have been found and isolated, wherein such small non-coding RNAs form a stable hairpin stem-loop secondary structure that is similar to the structure of a miRNA precursor, and wherein such secondary structure was found to contain two stem regions comprising at least 15-24 nucleotides in length that is similar to the structure of a mature miRNA, one of ordinary skill in the art would have embarked on the miRNA identification process with the already sequenced HSV-1 genome available in the art with a reasonably established anticipation that the artisan would identify at least one miRNA within the HSV-1 genomic sequence that contains numerous non-coding intergenic regions and would have reasonably identified nucleotides 118330-118351 located with one of the non-coding intergenic regions of the HSV-1 genome as a potential miRNA sequence with the help of a bioinformatics tool available in the art at the time the invention was made. Accordingly, the claimed invention taken as a whole would have been *prima facie* obvious at the time of filing.

Response to Arguments

Applicant's arguments filed on November 6, 2009 have been fully considered but they are not persuasive. Applicant argues that the claims are unobvious because "one of ordinary skill in the art at the time of filing would not reasonably expected success in identifying viral miRNAs from the teachings of the cited art." See page 10 of the reply filed on November 6, 2009. It is examiner's position that one of ordinary skill in the art would have reasonably expected to find miRNAs in a given sequenced viral genome, especially in the non-protein-coding regions of the HSV-1 genomic sequence that has been already sequenced and known in the art in view of the

ground of the instant 103(a) rejection applied herein in the instant Office action. Applicant argues that there is no reasonable expectation to find viral miRNAs because all of the previously known miRNAs are "genetically similar enough" such that the organisms from which miRNAs are isolated are "within the same branches of the phylogenic tree". See page 10 of the reply. However, applicant has failed to provide any compelling evidence showing that there would have been absolutely no possibility of finding miRNAs in viral genomic sequences just because viruses are not genetically related to the organisms that have been known to contain miRNAs. Nor has applicant provided any evidence or teaching showing that miRNAs are only found in genetically related organisms. Note that for obviousness under §103, "all that is required is a reasonable expectation of success", and it does not require "absolute predictability of success". See *In re O 'Farrell*, 853 F.2d 894, 7 USPQ2d 1673 (Fed. Cir. 1988) at 1681. Applicant argues that there would have been no expectation to find viral miRNAs "because viral genomes are too small and have little intergenic space to harbor hairpin precursors". See page 11 of the reply. Applicant has also pointed out pages 13-16 of the reply filed on February 26, 2008. It is noted that even without applicant-provided Tables in the reply filed on February 26, 2008, it was known in the art that miRNAs constitute about 1% of a given genome such as a mammalian genome or a *Drosophila* genome. See for example Lai et al. (*Genome Biology,* 2003, 4:1-20, citation of record). Furthermore, although the Tables show that the intergenic regions in the viral genome are relatively shorter than those in the phylogenetically related organisms, and thus miRNAs are predicted to be present less frequently in the viral genome relative to mammalian or invertebrate miRNAs, such findings do not whatsoever show the alleged impossibility of finding a miRNA in a given viral genomic sequence as stated by the declarant: "Dr. Honigman also

states that he previously doubted whether the small intergenic space of a virus would contain miRNAs and hairpin precursors." (emphasis added). See page 16 of the reply filed on February 26, 2008. Note that it is presumed to be nearly impossible for the declarant to have analyzed all of the intergenic viral genomic sequences known in the art for the presence/absence of miRNAs. As such, the declarant's "doubtful" statement merely amounts to an uneducated, extreme generalization of a wide array of various, different viral genomic sequences having differing lengths/spaces of intergenic regions. In addition, it is found that HSV-1 intergenic spaces (note that SEQ ID NO:2079 claimed in the instant case is a miRNA found in the HSV-1 genomic sequence, not EBV or HCMV or HPV listed in the Tables) contain sufficient length/space of nucleotide sequences that are able to harbor hairpin precursors. See the plenty of intergenic spaces/sequences within the HSV-1 genomic sequence cited in the instant rejection. Applicant asserts that only a "high" level of "creativity" that is "beyond the level of predictability required by the obviousness standard" would render the claims obvious. Contrary to applicant's assertion, the fact (acknowledged by applicant) that no miRNA in the viral genome was actually isolated in the art at the time of filing, together with the fact that viral genomic sequences contain a number of non-protein-coding intergenic sequences that are lengthy and spacious enough to contain potential hairpin precursors would have prompted a person of ordinary skill in the art to identify miRNAs located in the non-protein-coding intergenic sequences of a viral genome by utilizing art-recognized bioinformatics-based miRNA identification tools, because miRNAs in the viral genome had not been isolated or identified and thus an ordinary scientist whose normal desires are inarguably to make new discoveries would have been sufficiently motivated to explore the already sequenced viral genomic sequences for miRNA identification purpose. As such, no

illogically "high" level of "creativity" is deemed necessary to arrive at the claimed invention as asserted by applicant. It may be applicant's viewpoint that one cannot ever conceive of finding miRNAs in a viral genome without an abnormally high level of creativity; however, examiner disagrees with applicant's such viewpoint in view of the foregoing. Examiner believes that the response herein addresses all of applicant's concerns and arguments with regard to the 103(a) rejection applied in the last Office action.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting

ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 21, 33-34, and 52-53 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-6 of U.S. Patent in preparation for issuance from Application No. 10/604,942. Although the conflicting claims are not identical, they are not patentably distinct from each other because the instantly claimed broad "genus" claims are anticipated by the viral miRNA species claims drawn to a 24-mer of SEQ ID NO:37405 and a 116-mer of SEQ ID NO:37404. This is not a provisional rejection.

Claims 21, 33-34, and 52-53 are rejected on the ground of nonstatutory obviousness-type double patenting over claims 1-6 of a U.S. Patent in preparation for issuance from Application No. 10/604,943 because the instantly claimed subject matter is anticipated by the subject matter in the reference claims. Note that the reference claims are "species" (SEQ ID NOs:128, 131, 133, 477, 480, 482) encompassed by the broad "genus" claims of the instant application. This is not a provisional rejection.

Claims 21, 33-34, and 52-53 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-6 of U.S. Patent in preparation for issuance from Application No. 10/604,945. Although the conflicting claims are not identical, they are not patentably distinct from each other because the instantly claimed broad "genus" claims are anticipated by the viral miRNA species claims drawn to a 24-mer of SEQ ID NO:5264 and a 69-mer of SEQ ID NO:2194. This is not a provisional rejection.

Claims 21, 33-34, and 52-53 are rejected on the ground of nonstatutory obviousness-type double patenting over claims 1-6 of U.S. Patent in preparation for issuance from Application No. 10/604,984 because the instantly claimed subject matter is anticipated by the subject matter in the reference claims. Note that the reference claims are "species" (SEQ ID NOs:4642 and 1917) encompassed by the broad "genus" claims of the instant application. This is not a provisional rejection.

Claim 53 is rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claim 2 of U.S. Patent No. 7,217,807 B2. Although the conflicting claims are not identical, they are not patentably distinct from each other because the instantly claimed broad "genus" claim is anticipated by the viral miRNA species claim drawn to a 77-mer SEQ ID NO:14.

Claims 21, 33-34, and 52-53 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting over claims 26, 31, 33, and 35-37 of 10/709,739 because the

instantly claimed subject matter is anticipated by the subject matter in the reference claims. Note that the reference claims are "species" (SEQ ID NOs:4204050 and 117937) encompassed by the broad "genus" claims of the instant application.

Claims 21, 33-34, and 52-53 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting over claims 20, 22, 26, and 28-30 of 11/511,035 because the instantly claimed subject matter is anticipated by the subject matter in the reference claims. Note that the reference claims are "species" (SEQ ID NOs:906 and 3107) encompassed by the broad "genus" claims of the instant application.

Claims 21-34, 50, and 52-53 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting over claims 26-28 of 12/517,760 because the scope of the instant claims overlaps with the scope of the reference claims. Note that both the instant claims and the references claims embrace the entire genus of "viral" nucleic acids.

Response to Arguments

Applicant's reply filed on November 6, 2009 has been fully considered but it is not persuasive. Note that applicant has failed to properly address the supposed errors of the above-mentioned double patenting rejections (except the newly applied rejection over 12/517,760) that are reiterated herein, nor has applicant filed a signed terminal disclaimer for each of the applications/patents mentioned above. Hence, the rejections are hereby reapplied.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to DANA SHIN whose telephone number is (571)272-8008. The examiner can normally be reached on Monday through Friday, 7am-3:30pm EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Tracy Vivlemore (Acting SPE) can be reached on 571-272-2914. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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Examiner
Art Unit 1635

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